

# Hypoglycemic and antihyperlipidemic effect of aqueous leaves extract of *Ficus Religiosa* in alloxan induced diabetic rats



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## ABSTRACT

**Background:** Medicinal plants provide valuable therapeutic agents, with less adverse effects. A number of indigenous plants were claimed to be useful in the treatment of diabetes mellitus based on folk medicine. The purpose of this study was to examine the hypoglycemic and antihyperglycemic effect of aqueous leaves extract of *F. religiosa* in alloxan diabetes albino rats. **Aims and Objectives:** Therefore, the present thesis aim is in evaluating whether the hyperglycemic condition is related with hyperlipidemia and both these conditions could be controlled by indigenous preparations. **Materials and Methods:** The aqueous leaves extracts of *Ficus religiosa* (250 mg/kg) were administered orally for 21 days, in alloxan induced diabetic rats on Glucose, Lipid profile, Lipoproteins and Lipid metabolizing enzymes. **Result:** The aqueous leaves extract of *F. religiosa* induced significant improvement in glucose, serum lipids, lipoproteins concentration and lipid metabolizing enzymes activity (Lipase, HMG CoA reductase and LCAT). **Conclusion:** The present study indicates that the extract of *Ficus religiosa* exhibits lipid lowering, maintaining lipoproteins concentration and improve the activities of lipid metabolizing enzymes in hyperglycemic rats, by initiating the release of insulin. This study confirm the possible role of indigenous medicinal plants in the treatment of Diabetes.

**Key words:** *Ficus religiosa*, Lipid profile, Lipoproteins, LPL, HMG-CoA reductase, LCAT

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## INTRODUCTION

Medicinal plants continue to provide valuable therapeutic agents, both in modern medicine and in traditional system.<sup>1-4</sup> Medicinal plants also offer good prospects to finding new drugs particularly against conditions for which modern drugs are inadequate. Usually herbs are more accepted by the patients with less adverse effects. A wide variety of the traditional herbal remedies are used by diabetic patients, especially in the third world countries.<sup>5,6</sup>

*Ficus religiosa* is a large tree belonging to the family Moraceae. This tree is given the name of Budhidhidru or tree of wisdom by Buddhists. It is commonly known as Pipal and its leaves roots have been used for the treatment

of diabetes mellitus and to treat infertility in women.<sup>7</sup> It shows significant increase in serum insulin by initiating the release of insulin by beta cells of pancreas and having an extra pancreatic effect to possibly increase the number of insulin receptors.<sup>8</sup> This plant reduces the levels of serum triglyceride and total cholesterol in STZ-induced diabetic rats.<sup>9</sup> Dietary fibre content of foods namely, peepalbanti influenced total lipids, cholesterol, triglycerides and phospholipids of the liver to varying extents.<sup>10</sup> *Ficus religiosa* is rich in soluble fiber beta-glucan and it is contributes to lowering blood cholesterol level.<sup>11</sup>

The phytoconstituents of *F. religiosa* are reported as phenols, tannins, steroids, alkaloids and flavonoids,  $\beta$ -sitosterol-D-glucoside, vitamin K, n-octacosanol, methyl oleanolate,

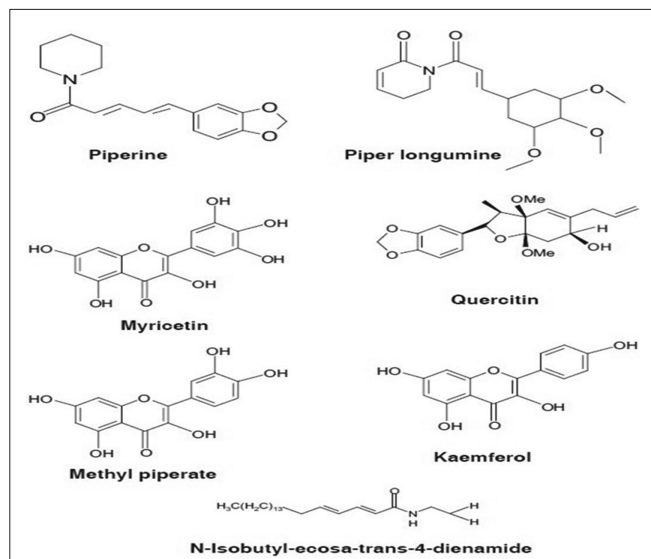
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lanosterol, stigmasterol, lupen-3-one, essential amino acids, (isoleucine, and phenylalanine), phytosterolin, flavonols namely kaempferol, quercetin, and myricetin, carbohydrate, protein, lipid, calcium, sodium, potassium, and phosphorus.<sup>12-15</sup>



The present work was undertaken to study the effect of the aqueous extract of the leaves of *Ficus religiosa* on the blood glucose level, lipid profile, serum lipoproteins and lipid metabolizing enzymes in normal and alloxan-diabetic rats. Acute toxicity was also studied to check the safety of these doses.

## MATERIALS AND METHODS

The fresh leaves of *F. religiosa* were collected locally. Plants were confirmed by Taxonomist from Department of Botany, Institute of Science, Nagpur. Fresh leaves of *F. religiosa* were washing carefully with water and mechanically crushed with distilled water using Soxhlet at boiling temperature (100°C) up to 36 hrs. The extract was filtered and concentrated in rotating evaporator under reduced pressure to obtained semisolid material which was then lyophilized to get a powder and store in air tight bottle.

### Doses

250 mg/kg body wt/day of powder of *F. religiosa* dissolved in 5ml of distilled water given to experimental rats through metal canula attached to syringe.

### Selection of animals

Adult male albino rats weighing from 150-200 grams were used for the experiments carried out in the present study. All rats were kept at room temperature of 24-28°C in the animal room of the Post Graduate Department of Biochemistry, LIT Campus. Nagpur. All the animals were

maintained on the Hindustan Lever diet and water as ad libitum during the experimental period. A total of 36 rats were segregated into 6 groups of six animals each.

### Induction of diabetes

For induction of diabetes in the experimental albino rats, alloxan monohydrate supplied by Loba Chemicals, Bombay, India, was used.

The animals were divided in 5 groups. The animals of group I was served as nondiabetic controls. The animals of group II, III, IV and V were fasted for 16 hours but had free access of water and diabetic condition was induced in them with a single injection of alloxan monohydrate (18 mg/100 gm body weight) prepared in sterile normal saline given intraperitoneally, while the normal nondiabetic animals were injected with equal volume of saline. After 72 hours of alloxan injections the diabetic condition was confirmed by estimating plasma glucose level in group II. Similarly, by estimating serum lipids, the hyperlipidemic condition was confirmed in the animals of same group. Henceforth, the animals injected with alloxan were divided in groups III, IV and V for drug treatment study. The diabetic animals of group III served as alloxan diabetic controls. The diabetic animals of group IV and V were treated with indigenous preparation and oral hypoglycemic drugs. The drug was scheduled for twenty one days.

At the end of experimental period, the animals were deprived of food overnight and sacrificed by decapitation at the end of respective experimental periods. Blood was collected in fluoride bulbs for estimation of plasma Glucose and in plain bulbs for serum estimations. Serum from different groups were either analyzed immediately or stored in freeze until analyzed for different lipid parameter.

### Analytical methods

Autozyme kits were obtained from Ranbaxy and Accurex Biomedical PVT LTD. diagnostic company.

Plasma glucose, T. cholesterol, Triglyceride, phospholipids, free fatty acids, HDL-cholesterol, Lipoprotein lipase, HMG CoA reductase activity (HMG CoA/Mevalonate ratio), LCAT activity (Free cholesterol/Esterified cholesterol ratio).<sup>16-24</sup>

### Statistical analysis

All the data were statistically evaluated and the significance calculated using student's test. All the results were expressed as mean  $\pm$  SEM

## RESULTS

The Aim of this study was to examine the effect of single dose (250 mg/bwt) of *Ficus religiosa* for 21 days in

alloxan induced diabetes in rats showed hypoglycemic and antihyperlipidemic activity.

The result revealed in Table 1, that the extract of *F. religiosa* had good antidiabetic effect. It showed moderate decrease in the blood glucose, serum cholesterol, triglyceride and increase phospholipids levels as compared to other test materials.

The increased VLDL-C and LDL-C levels with decrease in HDL-C concentration in alloxan induced diabetic rats shown significant decreased in VLDL-C and LDL-C with increase in concentration of HDL-C after treatment with *T. dioica*. Thus this drug is helpful for restore in the decrease HDL-C level in alloxan induced diabetic animals as given in Table 2.

Table 3 shows the significant improvement in the activity of lipid metabolizing enzymes (Lipoprotein lipase, HMG CoA reductase and Lecithin cholesterol acyl transferase) after treatment with *T. dioica* in alloxan induced diabetic rats.

## DISCUSSION

Diabetes mellitus is one of the most common chronic disease and is associated with hyperlipidemia and co-morbidities such as obesity, hypertension. Hyperlipidemia is a metabolic complications of both clinical and experimental diabetes.<sup>25</sup> Alloxan, a beta cytotoxin, induces “chemical diabetes” (alloxan diabetes) in a wide variety of animal species by damaging the insulin secreting pancreatic -cell, resulting in a decrease in endogenous insulin release, which paves the ways for the decreased utilization of glucose by the tissues.<sup>26</sup>

In Indian traditional system of medicine, *Ficus religiosa* (Family Moraceae) is prescribed for the treatment of diabetes mellitus. Previous reports demonstrated that the administration of several herb extract could restore the changes in the activities of serum enzymes, lipid profiles and oxidative stress.<sup>1,2,4</sup>

The present study includes the efficacy of aqueous extract of *Ficus religiosa* for their hypoglycemic and

**Table 1: Effect of aqueous extract of *F. religiosa* on plasma glucose and serum lipid profiles (mg/dl) in alloxan induced diabetic rats**

Group	Treatment	Pl.Glucose	T.Cholesterol	Triglyceride	Phospholipids	FreeFatty Acid
Grp. I	Normal	84.37±0.26	90.5±1.18	65.1±0.06	130.5±0.04	22.53±0.15
Grp. II	D. Control	254.47±0.71***	137.8±1.54*	83.38±0.15***	113.43±0.08****	27.82±0.03****
Grp. III	D. control	274.9±0.21	172.82±0.31	96.4±0.16	86.81±0.27	33.2±0.21
Grp. IV	D+F. religiosa	100.08±0.42***	104.75±0.17**	74.33±0.88*	117.83±0.48****	24.93±0.05*
Grp. V	D+Tolbutamide	115.3±0.29****	100.45±0.17 <sup>NS</sup>	67.58 0.16 <sup>NS</sup>	125.27±0.20***	22.73±0.18 NS

Values are given as mean±SEM (n=6). Values were statistically significant at \*P<0.05, \*\*P<0.02, \*\*\*P<0.01, \*\*\*\*P<0.001. Normal Vs Diabetic control and Diabetic control Vs Diabetic treated albino rats

**Table 2: Effect of Herbal preparation of *F. religiosa* on serum lipoproteins (mg/dl) in alloxan induced diabetic rats**

Group	Treatment	HDL-C	VLDL-C	LDL-C
Grp. I	Normal	41.5±0.06	13.02±0.01	35.98±0.06
Grp. II	D. Control	35.57±0.06****	16.68±0.02***	85.55±0.09***
Grp. III	D. control	30.55±0.22	19.28±0.03	122.98±0.50
Grp. IV	D+F. religiosa	39.88±0.02****	15.18±0.06**	41.18±0.42*
Grp. VI	D+Tolbutamide	42.66±0.44*	13.48±0.03 <sup>NS</sup>	44.11±0.25 <sup>NS</sup>

Values are given as mean±SEM (n=6). Values were statistically significant at \*P<0.05, \*\*P<0.02, \*\*\*P<0.01, \*\*\*\*P<0.001. Normal Vs D. control and Diabetic Control Vs Diabetic treated albino rats

**Table 3: Effect of Herbal preparation of *F. religiosa* on lipid metabolizing enzymes in alloxan induced diabetic rats**

Group	Treatment	LPL activity $\mu\text{M}/\text{ml}/\text{min}$	HMG CoA reductase	LCAT activity (Fc/Ec ratio)		
				FC	EC	FC/EC
Grp. I	Normal	0.296±0.001	1.65±0.06	22.95±0.13	67.55±0.13	0.339±0.002
Grp. II	D. Control	0.261±0.001***	3.59±0.06****	36.53±0.16***	99.27±0.16**	0.389±0.002c
Grp. III	D. Control	0.196±0.0008	3.75±0.02	49.93±0.02	122.9±0.02	0.406±0.0003
Grp. IV	D+F. religiosa	0.245±0.0004***	2.01±0.10***	27.2±0.02***	68.77±0.28*	0.350±0.0003*
Grp. VI	D+Tolbutamide	0.292±0.0008 <sup>NS</sup>	1.71±0.16 <sup>NS</sup>	26.2±0.07 <sup>NS</sup>	74.22±0.03 <sup>NS</sup>	0.351±0.0004***

HMG CoA activity mentioned as (HMG CoA/Mevalonate ratio). Values are given as mean±SEM (n=6). Values were statistically significant at \*P<0.05, \*\*P<0.02, \*\*\*P<0.01, \*\*\*\*P<0.001. Normal Vs D. control and Diabetic Control Vs Diabetic treated albino rat

hypolipidemic activities in alloxan induced diabetes in rats showing a good glycemic control also corrects the abnormalities in serum lipid profile associated with diabetes. For the assessment of hypoglycemia the parameters considered were peak level and duration of hypoglycemia. However the duration of action was considered as the most important parameter for evaluation of efficacy. Similarly, the emphasis was also laid down on the ability of water extract of *F. religiosa* to keep control over the serum lipoproteins.

In view of the similarity between the effects of tolbutamide and *Ficus religiosa*, it may be likely that the hypoglycaemic effect of *Ficus religiosa* also be mediated through the release of insulin from the pancreatic cells. In the present study the significant hypoglycemic action of aqueous extract of *Ficus religiosa* may be by potentiating the insulin effect of plasma by increasing either the pancreatic secretion of insulin from  $\beta$ -cells of islets of langerhans or its release from bound form.<sup>27</sup>

It was reported that hypertriglyceridemia, hypercholesterolemia and reduced HDL level were commonly seen in diabetes<sup>4,28</sup> due the impaired removal of triglycerides from the circulation or its entry into the circulation.<sup>29</sup> The present results showed the significant decrease in level of serum lipids were observed with daily treatment with *Ficus religiosa*.

Earlier study showed that lipid lowering activity of *Ficus religiosa* is due to soluble polysaccharide beta-glucan. The dietary fibre influenced total lipids, cholesterol, triglycerides and phospholipids of the liver to varying extents, and it contributes to lowering blood cholesterol level.<sup>30,11</sup> Glucan is bind bile acids in the small intestine, these bile acids are synthesized in the liver from cholesterol and secreted into the small intestine. The fiber-bile acids complex prevents bile acids from being reabsorbed from the small intestine, enhancing the secretion of bile acids, to replace the lost acids; cholesterol is drawn from the circulation for the production of bile acids, thereby reducing the blood cholesterol levels. Other proposed mechanism for the reduction of blood cholesterol by the fibers include, the soluble polysaccharides were fermented in the colon. This molecule is absorbed and taken to the liver where it has inhibitory effect on the activity of hydroxy methyl glutaryl CoA reductase, thus reducing denovo cholesterol synthesis.<sup>31</sup> Insulin is potent inhibitor of lipolysis, since it inhibits the activity of the hormone sensitive lipases in adipose tissue and suppresses the release of free fatty acid.<sup>32</sup> During diabetes, enhanced activity of this enzyme increases lipolysis and releases more free fatty acids in to the circulation.<sup>33</sup> Increased fatty acids concentration also increases the  $\beta$ -oxidation of fatty acids, producing

more acetyl CoA and cholesterol during diabetes. Lipid phosphorus was found to be decreased significantly in uncontrolled diabetes, it is suggested that the phospholipids are affected by hyperlipidemia.<sup>25</sup> It has been pointed out that lipids are discharged from fat depot in unusual quantities in respond to urgent body need for fuel substrate. Infact, the metabolic disturbances of diabetes interferes with the process by which fatty acids are transferred to cholesterol and attached to protein resulting their accumulation in plasma.<sup>34</sup> The active principals of extract of *F. religiosa* may have insulin-releasing effect, through which it may favorably modify the triglyceride and cholesterol level as well.

Lipoprotein pattern provides a fair index of serum cholesterol and triglyceride level. Since maximum cholesterol and triglyceride were found to be associated with lipoproteins (LDL and VLDL), any change in cholesterol and triglyceride content of blood influences the serum concentration of LDL and VLDL lipoprotein. These lipoproteins serve as transport vehicle for circulating lipids in blood.

HDL especially plays an important role by accepting cholesterol, phospholipids and apoproteins that are released during degradation of triglycerides. HDL exerts its apparent protective role against the development of hypercholesterolemia.<sup>35</sup> Its concentration is regulated by an insulin dependent enzyme lipoprotein lipase. Hence inadequate availability of insulin decreases the enzyme LPL and may contribute to the lowering of serum HDL by increase removal of HDL cholesterol from blood of diabetic animals. Increased in activity of serum lipase was observed which leads into increase breakdown of serum triglyceride. However, serum free fatty acid level show a remarkable decrease after treatment of drug. This may suggest that the extract of *F. religiosa* might be either enhancing the uptake of free fatty acid by a adipose tissue or liver and its further incorporation into triglyceride in those tissues.

The decreased HMG CoA reductase activity could be due to an increased cholesterol excretion and decreased cholesterol absorption through the gastrointestinal tract. Thus the decreasing cholesterol levels in the body under the influence of *T. dioica* could have enhanced the enzymatic activity by a positive feedback mechanism.<sup>36</sup>

HDL plays a central role in reverse cholesterol transport because it not only promotes the efflux of cholesterol from peripheral tissues but also the major site for the esterification of cholesterol by LCAT. LCAT modulates cholesterol transfer from lipoproteins and cell membrane to HDL. Therefore decreased activity of LCAT promotes

the accumulation of free cholesterol to cell membrane and of remnant lipoprotein in plasma, both factors being strongly related to Atherosclerosis.<sup>37,38</sup>

From this study we can conclusively state that the extract of *F. religiosa* has beneficial effects on blood glucose level as well as rectifying hyperlipidemia due to diabetes. It confirmed that the active principles present in the aqueous extract of *F. religiosa* might be responsible for highly significant hypoglycemic and hypolipidemic and significant improvement in lipid metabolizing enzyme activity. But further pharmacological screening is necessary to pin point the possible mechanism of action.

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**Authors Contribution:**

**MP** - Concept and design of the study, collected data, literature search, statistically analyzed and interpreted, prepared first draft of manuscript; **MGM** - Review of study, review of literature, critical revision of the manuscript.

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